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and DNA polymerases that have been modified to eliminate a 3'-5' exonuclease activity selected from the group consisting of the exo (-) versions of  $\phi$ 29 DNA polymerase, Klenow fragment, Vent and Pfu DNA polymerases.

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D1  
59. (Amended) The process of claims 38 wherein said multiple primers are a mixture of primers sensitive to exonuclease activity and resistant to exonuclease activity.

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60. (Amended) The process of claims 38 wherein a linear DNA target is used instead of said ATC.

61. (Amended) The process of claim 56 wherein said DNA polymerase is  $\phi$ 29 DNA polymerase.

### REMARKS

Claims 1-15 and 20-64 are pending in the case. All claims have been rejected.

### Claim Objections

Claims 59 and 60 have been objected to as being in improper form because of multiple dependent language. In response, Applicants have amended these claims to depend only from claim 38.

### Rejection Under 35 U.S.C. §112

Claims 50, 56, 59 and 60 stand rejected under 35 U.S.C. 112, second paragraph,

as indefinite. In response, Applicant has amended these claims to make them more definite. In claim 50, "said" has been deleted and the claim now reads "the 3'-terminal nucleotide of the primer." Claim 56 was amended to remove the "such as" language and the claim now reads the same as corresponding claim 56 of the Lasken Patent (U.S. 6,323,009 B1). Claims 59 and 60 had depended from claim 56 and have been amended to depend from claim 38 only to avoid any improper multiple dependence. Thus, this ground of rejection is believed to have been overcome in light of the recited amendments.

### **Rejection Under 35 U.S.C. §102**

Claims 1, 2, 5-7, 10, 11, 20, 22-24, 26-29, 31, 33, 35-40, 42, 44-45, 48, 49, 51-54, and 62-64 were rejected under 35 U.S.C. 102(b) as being anticipated by Lizardi (U.S. Pat. No. 5,854,033 – Lizardi-1). In response, Applicant has cancelled claims 2, 10, 26, 28, and 62-64. In addition, Applicant has amended claim 1 (the only independent claim now remaining) to recite use of random primers that bind to the ATCs and using dNTPs that render the TS-DNA product resistant to exonuclease activity. Because all other pending claims are dependent from claim 1, and because Lizardi 1 does not disclose use of random primers, this ground of rejection has been overcome and Lizardi 1 does not anticipate these claims.

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Claims 1, 2, 5-7, 10, 11, 20, 22, 23, 26, 36, 37, 38, 51, 52, and 62-64 were rejected under 35 U.S.C. 102(e) as being anticipated by Kingsmore et al (U.S. 2001/0041340 A1). In response, Applicant has cancelled claims 2, 10, 26, and 62-64. In addition, Applicant has amended claim 1 to recite use of random primers, which is not disclosed in Kingsmore et al. Consequently, claim 1 (and all claims dependent therefrom) is not anticipated by this reference and this ground of rejection has been overcome since the reference does not disclose all elements of the claims.

### **Rejection Under 35 U.S.C. §103**

Claims 8 and 9 were rejected as obvious over Lizardi 1 in view of Sorge (U.S. Pat. No. 5,599,921). These claims are directed to use of hexamer and octamer primers, which are not disclosed by Lizardi-1, but such primers are disclosed by Sorge. However, Applicant responds that in view of the amendment to claim 1 to recite use of random primers, this ground of rejection has been overcome. Sorge discloses use of primers with sequences "substantially complementary" to the target DNA (at column 4, lines 27-36, and at column 12, lines 8-18) and not random primers. Thus, claims 8 and 9 should be allowable as dependent from claim 1.

Claims 3, 12-14, 21, 25, 60 and 61 were rejected under 37 U.S.C. 103(a) as obvious over Lizardi-1 and further in view of Lizardi-2 (U.S. Pat. No. 6,124,120). In response, Applicant has cancelled claim 3 and has amended claim 1 (from which the other claims depend either directly or indirectly) to recite use of dNTPs that render the resulting TS-DNA product resistant to exonucleases. This is not taught or suggested by either of the Lizardi references and thus they do not render the remaining claims unpatentable.

Claim 4 was rejected under section 103 based on Lizardi-1 and Lizardi-2. Claim 4 has been cancelled.

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Claim 15 was rejected under section 103 as unpatentable over Lizardi-1 and Lizardi-2 on grounds that, although neither teaches a denaturation step, it is common knowledge to use one. Applicant responds that the amendment to claim 1 renders claim 15, which depends from claim 12 or 13, both of which depend from claim 1, patentable over these references because amended claim 1 is patentable over these references.

Claims 32, 41, 46, 47 and 59 were rejected under section 103 as unpatentable over Lizardi-1 and further in view of Skerra (1992) on grounds that Lizardi-1 teaches use of a polymerase with exonuclease activity while Skerra teaches use of a phosphorothioate

nucleotide at the 3'-end of a primer to make them exonuclease resistant. In response, Applicant has amended claim 1 to incorporate use of a dNTP that makes the resulting TS-DNA product resistant to exonuclease activity. Use of exonuclease resistant primers is only recited in dependent claim 38 and claims dependent therefrom. Thus, claims 26 and 28 have been cancelled and their limitations incorporated into amended claim 1. Claim 28, and claims dependent therefrom, specifically recited use of a dNTP of claim 26 that would make the resulting TS-DNA resistant to exonuclease activity. Thus, the above claims should be patentable over these references.

Claims 30, 34 and 43 were rejected under section 103 as unpatentable over Lizardi-1 in view of Cummins et al (1996). In response, Applicant has cancelled these claims.

Claims 55 and 56 were rejected under section 103 as unpatentable over Lizardi-1 in view of Sorge et al (U.S. Patent No. 5,556,722). In response, Applicant has amended claim 1 from which claims 55 depends (claim 56 depends from claim 55) so that these claims now incorporate the limitations of claim 1 as amended, which limitations are drawn from now cancelled claims 26 and 28, thereby making claim 55 patentable over Lizardi-1 in view of Cummins et al, since the latter references do not teach use of a dNTP that renders the TS-DNA product resistant to nucleases.

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Claims 57 and 58 were rejected under section 103 as unpatentable over Lizardi-1 and Lizardi-2 since these claims are directed to use of a reverse transcriptase with and without RNA. Applicant responds that the amendment of claim 1 to recite use of a dNTP that causes the product to be resistant to nucleases, as well as multiple primers, renders claims 57 and 58 patentable over these references since they in no way suggest such limitations.

Claims 8 and 9 were rejected under section 103 as unpatentable over Kingsmore et al in view of Sorge et al (U.S. 5,599,921) because they relates to multiple primers that are hexamers and octamers. However, Sorge et al teach only primers that are

substantially complementary to the target DNA (as already noted) and therefore does not suggest use of random primers. Likewise, as the Examiner concedes later in the Office Action (at page 12), Kingsmore et al do not teach random primers either. Consequently, since claim 1 as amended now recites use of random primers, these references do not render claim 1, or claims dependent therefrom, as unpatentable.

Claims 3, 12-14, 21, 25, 60 and 61 were rejected under section 103 as unpatentable over Kingsmore et al in view of Lizardi-2. However, the Examiner concedes that Kingsmore et al does not teach random primers while Lizardi-2 teaches use of random primers and the use of multiple primers. In response, Applicants have cancelled claim 3 and have amended claim 1, from which the other claims depend, to recite the limitations of claims 3, 26 and 28, the latter dependent claims having been cancelled. Thus, this ground of rejection has been overcome.

Claim 4 was rejected under section 103 as unpatentable over Kingsmore et al in view of Lizardi-2. In response, claim 4 has been cancelled.

Claim 15 was rejected under section 103 as unpatentable over Kingsmore et al in view of Lizardi-2. In response, claim 4 has been cancelled. Claim 15 depends from claims 12 or 13, which depend from claim 1. Claim 1 has now been amended to recite use of random primers as well as dNTPs that render the product TS-DNA resistant to nucleases. Consequently, these references have been overcome and the claim should be allowable.

Claims 28, 29, 31-33, 35, 40-42, 44-47 and 59 were rejected under section 103 as unpatentable over Kingsmore et al in view of Skerra. In response, Applicant has amended claim 1, from which the other claims depend either directly or indirectly, to recite use of random primers as well as dNTPs that render the TS-DNA product resistant to nucleases. These elements are not suggested by the cited references and this ground of rejection has been overcome. In addition, claim 59 has been cancelled.

Claims 30, 34 and 43 were rejected under section 103 as unpatentable over

Kingsmore et al in view of Cummins et al. These claims recite types of nuclease activity. However, in response, Applicant has amended claim 1, from which the other claims depend either directly or indirectly, to recite use of random primers as well as dNTPs that render the TS-DNA product resistant to nucleases. These elements are not suggested by the cited references regardless of the source or type of nuclease activity so that this ground of rejection has been overcome.

Claims 55 and 56 were rejected under section 103 as unpatentable over Kingsmore et al in view of Sorge et al (the '722). In response, Applicant has amended claim 1, from which claim 55 depends (claim 56 depends from claim 55), to recite use of random primers as well as dNTPs that render the TS-DNA product resistant to nucleases. These elements are not suggested by the cited references regardless of the type of polymerase used and this ground of rejection has been overcome.

Claims 57 and 58 were rejected under section 103 as unpatentable over Kingsmore et al in view of Lizardi-2. In response, Applicant has amended claim 1, from which these claims depend, to recite use of random primers as well as dNTPs that render the TS-DNA product resistant to nucleases. These elements are not suggested by the cited references regardless of the use of RNA and/or reverse transcriptase and this ground of rejection has been overcome.


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### **Rejection Based on Double Patenting**

Claims 1-15 and 20-64 have been rejected for obviousness-type double patenting based on claims 1-67 of U.S. Patent No. 6,323,009 B1. Because Applicant has amended claim 1, from which all of the other claims of the application depend either directly or indirectly, to recite use of random primers as well as dNTPs that render the TS-DNA product resistant to nucleases and regardless of the source of the ATC or any preferential amplification over genomic DNA, Applicant believes that the claims of the present

application are no longer a species of the claims of the '009 patent and thus this ground of rejection should be withdrawn.

Applicant encloses herewith a Request for a three month extension of time along with the required fee for a small entity. The Commissioner is authorized to charge payment of any additional filing fees required under 37 CFR 1.16 associated with this communication or credit any overpayment to Deposit Account No. 03-0678.

<p align="center"><b><u>EXPRESS MAIL CERTIFICATE</u></b></p> <p>Express Mail Label No. EF010573935US</p> <p>Deposit Date: 12 June 2002</p> <p>I hereby certify that this paper and the attachments hereto are being deposited today with the U.S. Postal Service "Express Mail Post Office To Addressee" service under 37 CFR 1.10 on the date indicated above addressed to:</p> <p align="center">Commissioner for Patents Washington, DC 20231</p> <p> <u>6/12/02</u> Alan J. Grant, Esq.      Date</p>
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Respectfully submitted,



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## AMENDED CLAIMS

1. (Amended) A process for selectively amplifying nucleic acid sequences comprising ~~forming a mixture comprising:~~ contacting multiple single stranded non-circular random oligonucleotide primers (P1), one or more amplification target circles (ATCs), a DNA polymerase and multiple deoxynucleoside triphosphates (dNTP), under conditions promoting said contacting, wherein said one or more ATCs hybridizes ATC ~~binds~~ to more than one of said multiple P1 primers, and wherein said conditions promote replication of said amplification target circle by extension of the P1 primers to form multiple tandem sequence DNA (TS-DNA) products and wherein said multiple deoxynucleoside triphosphates (dNTP) are selected from the group consisting of dTTP, dCTP, dATP, dGTP, dUTP, a naturally occurring dNTP different from the foregoing, an analog of a dNTP, and a dNTP having a universal base and wherein at least one nucleotide renders the TS-DNA resistant to nuclease activity following incorporation thereinto.

29. (Amended) The process of claim 28 1 wherein said at least one nucleotide is a phosphorothioate nucleotide.

30. (Amended) The process of claim 28 1 wherein said nuclease activity is due to an endonuclease.

31. (Amended) The process of claim 28 1 wherein said nuclease activity is due to an exonuclease.

34. (Amended) The process of claim 28 1 wherein said nuclease activity is due to a contaminating nuclease.

35. (Amended) The process of claim 28 1 wherein said at least one nucleotide is a modified nucleotide.

50. (Amended) The process of claim 49 wherein ~~said~~ the 3'-terminal nucleotide of ~~said~~ the primer can be removed by 3',5'-exonuclease activity.

56. (Amended) The process of claim 55 wherein said DNA polymerase is selected from the group consisting of DNA polymerases lacking a 3'-5' exonuclease activity, such as Taq, Tfl, and Tth DNA polymerase, Eukaryotic DNA polymerase alpha, and DNA polymerases that have been modified to eliminate a 3'-5' exonuclease activity ~~such as selected from the group consisting of the~~ exo (-) versions of  $\phi$ 29 DNA polymerase, Klenow fragment, Vent and Pfu DNA polymerases.

59. (Amended) The process of claims ~~38-56~~ 38 wherein said multiple primers are a mixture of primers sensitive to exonuclease activity and resistant to exonuclease activity.

60. (Amended) The process of claims ~~38-56~~ 38 wherein a linear DNA target is used instead of said ATC.

61. (Amended) The process of claim 60 56 wherein said DNA polymerase is  $\phi$ 29 DNA polymerase.

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